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Steffen, Christian ; Schaepman, Michael ; Hardmeier, Thomas ; Schweitzer, Wolf

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## CASE REPORT

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# Digital 3D reconstruction of two parahissian accessory bundles in a case of Wolff-Parkinson-White syndrome

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**Abstract** Three-dimensional reconstruction of digitized histological serial sections of the cardiac conduction system yielded two accessory pathways in a case of a 24-day-old male infant who died after a short period of illness with ECG findings of Wolff-Parkinson-White syndrome. In infants, the differential diagnosis of possible accessory pathways connecting the AV conduction system, atrial or ventricular septum includes dispersed conduction system tissue without connecting features. This is why three-dimensional reconstruction is necessary in order to refute or establish connectivity of cell groups as found in histological serial slice images.

**Keywords** Wolff-Parkinson-White syndrome · Electrocardiography · Histology · Reconstruction · Forensic pathology · Cardiac death

## Introduction

Accessory bundles are involved in a range of arrhythmias and may play a significant role in the pathophysiology of natural or violent death. Even though the reported incidence of 'sudden death' among adults with known Wolff-

Parkinson-White (WPW) syndrome is as low as 0.0015 per patient year [1], accessory pathways may go undiagnosed before facilitating serious arrhythmia. Torner [2] reported that out of 23 patients with WPW syndrome successfully resuscitated from VF (ventricular fibrillation), 6 patients had their first symptomatic arrhythmia ever. Morphologically, the incidence of Mahaim bundles was found to be higher in babies without a concise cause of death [3]. Accessory bundles were also implied as the cause of arrhythmia in accidental deaths [4].

Demonstration of accessory bundles depends on the proof of connectivity of conduction system tissue strands found in the atrioventricular region [5], which can be differentiated from unconnected tissue strands by examining a 3D (three-dimensional) reconstruction of such muscle cell islands for connectivity [6]. Other conduction system pathologies, such as fibrosis [7], calcium deposits or fatty infiltration of conduction system structures [8], can be recognized without a 3D reconstruction. We report digitally reconstructed histological findings of parahissian accessory bundles in a 24-day-old male who died after a short period of illness and was diagnosed with probable WPW syndrome based on post-resuscitation ECG (electrocardiogram) results.

## Case history

A 24-day-old male infant died on April 28th 1980. 6 days prior to death the symptoms were thin stool and poor fluid intake. 2 days prior to death, cool skin and some vomiting were detected and 1 day prior, palpitations occurred. On what eventually was the last day, he was apathetic, sweating, and tachycardic. The general practitioner admitted the child to the University Hospital of Zurich. The infant arrived in an unconscious state with fixed and dilated pupils, without heart action, and without signs of dehydration.

Resuscitation attempts resulted in regular cardiac action and peripheral pulse after 10 min. ECG then showed a PQ-time of 0.09–0.10 s (normal [9], possibly shortened but not diagnostic in infants under 12 months [10]) and a QRS width of 0.09 s (increased [9]). A  $\Delta$ -wave was most markedly noticeable in V1 and V2, and there was a left anterior hemiblock. Heart rate alternated between normal and tachycardic (over 200 bpm) with broad complexes. After an electroencephalogram produced a flat line, life support was turned off 10 h after admission to hospital.

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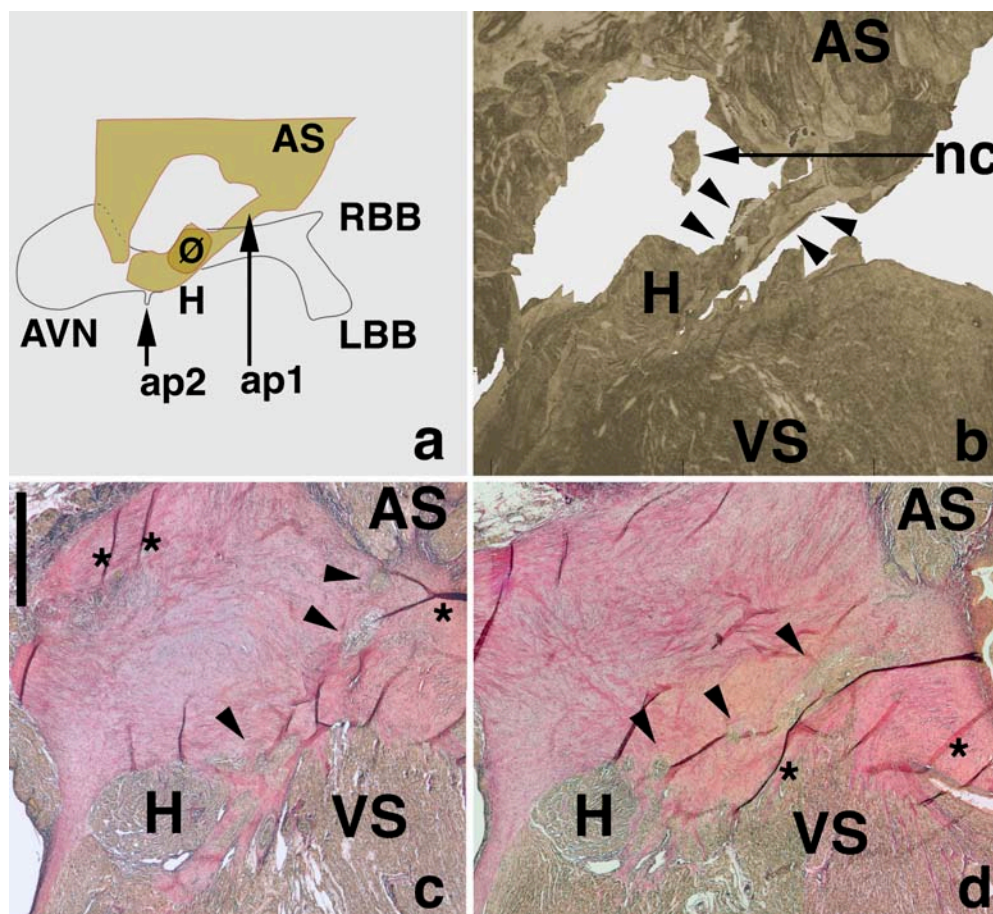
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**Fig. 1a–d** Reconstruction of atriofascicular pathway (*ap1*). **a** The diagram shows the position of the 3D reconstruction of serial sections (yellow, as seen in Fig. 1b) in relation to the atrioventricular part of the conduction system (AVN atrioventricular node, *H* His bundle,  $\emptyset$  cross section through His bundle, *RBB* right bundle branch, *LBB* left bundle branch, *ap1* atriofascicular pathway, *ap2* fasciculoventricular pathway). **b** Digital 3D reconstruction of serial sections easily discerns accessory pathway connecting atrium with His bundle (arrowheads) from non-connecting tissue strands (one of them labeled *nc*). **c, d** Histological serial sections of the atrioventricular part of the cardiac conduction system containing the His bundle (*H*) with conduction system tissue dispersed throughout the fibrous body contributing to atriofascicular bundle (arrowheads). *AS* atrial septum, *VS* ventricular septum, scale bar 1 mm



The boy had been a second-born with a birth weight of 3650 g (~90%) after a regular pregnancy of a healthy mother. He had received light therapy due to hyperbilirubinemia on days 5 and 6 and initial development was normal. The family history did not contain any instances of relatives succumbing to sudden death or cardiac arrhythmia. The archived patient's history did not contain ECG curve prints.

Autopsy findings did not show congenital malformations and were not conclusive as to the cause of death. Total body weight was 4100 g (50–75% normal), body length was 58 cm (97%), and head circumference measured 37.5 cm (50–75%). With the exception of the thymus (18.7 g, normal 6.6±4.9 g), organ weights were normal [11].

## Material and methods

The posterior, lateral and septal atrioventricular junction was processed into a set of 1,300 histological serial sections spaced 50  $\mu$  and stained with van Gieson-elastin stain. Histological serial sections showed cell nests or cell strands possibly contributing to accessory bundles (Figs. 1c,d and 2c,d, arrowheads) that were located over a range of 25 serial sections around the His bundle (Figs. 1 and 2 *H*). No other signs of pathology were identified.

These 25 serial sections and a scale slide were digitized using a microscope-mounted camera (Jenoptik, Eching, Muenchen, Germany). The image series was manually co-registered into a three-dimensional data volume [12] using the first image as reference and manually positioning subsequent images through rotation and shifting. Embedding of cut tissue caused minor tissue folds (Fig. 1c,d, labeled '\*') measuring around 5–10  $\mu$  in width, evenly distributed throughout the fibrous body. The co-registration error of the image

series could not be measured directly, so control points were placed manually onto a number of anatomic structures with a known coherence in the z-axis (such as endocardial surface or vessels). Control point tracking yielded an in-plane deviation of 5–15  $\mu$ , which we judged to be sufficiently small in order to examine structures in the 100–150  $\mu$  size range.

Myocardial tissue was segmented manually from fibrous tissue in each digital image employing slice-wise validation against microscopy. Volume rendering in IDL (Interactive Data Language, Research Systems, Boulder, Colorado) resulted in three-dimensional reconstructions that were clipped in order to expose identified accessory pathways individually (Figs. 1b and 2b).

## Results

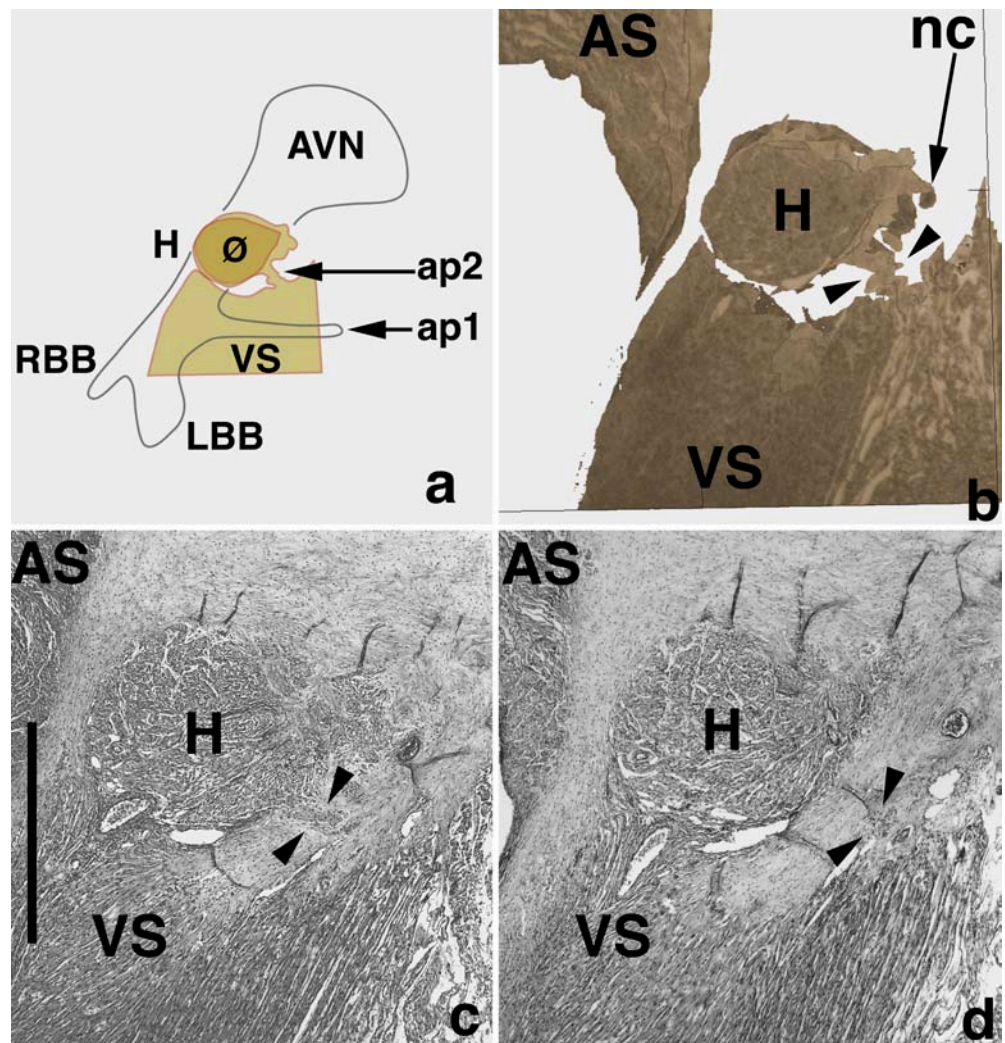
Visual inspection of the 3D reconstructions resulted in the identification of two accessory pathways with a parahissian location in the posterior atrioventricular septum.

One accessory pathway was an atriofascicular bundle (anatomically termed 'James' bundle [13], functionally termed Mahaim bundle [14], Fig. 1b, arrowheads) connecting the posterior atrial septum (Fig. 1b, *AS*) with the His bundle (Fig. 1b, *H*) with a smallest diameter of 100  $\mu$ . Dispersed or non-connecting conduction system tissue was identified in various locations (labeled *nc* in Fig. 1b and 2b).

A second accessory bundle was a fasciculoventricular bundle (anatomically and functionally termed Mahaim



**Fig. 2a–d** Reconstruction of fasciculoventricular pathway (*ap2*). **a** Diagram showing position of the 3D reconstruction of serial sections (yellow, as seen in Fig. 2b) in relation to the atrioventricular part of the conduction system (AVN atrioventricular node, *H* His bundle,  $\emptyset$  cross section through His bundle, *RBB* right bundle branch, *LBB* left bundle branch, *ap1* atriofascicular pathway, *ap2* fasciculoventricular pathway). **b** Digital 3D reconstruction of serial sections differentiates accessory pathway connecting His bundle with ventricle (*arrowheads*) from non-connecting tissue strands (one of them labeled as *nc*). **c, d** Histological serial sections of the atrioventricular part of the cardiac conduction system containing the His bundle (*H*) with conduction system tissue dispersed throughout the fibrous body contributing to fasciculoventricular bundle (*arrowheads*). *AS* atrial septum, *VS* ventricular septum, scale bar 1 mm



bundle [13], about 125  $\mu$  diameter, Fig. 2b, *arrowheads*) that connected the penetrating bundle of His (Fig. 2b, *H*) with the ventricular septum (Fig. 2b, *VS*).

## Discussion

WPW is a diagnosis based on ECG features from which localization of accessory pathways can be inferred. In this instance, observed  $\Delta$ -wave features are more likely to be based on a septal or parahissian than a parietal location of accessory pathways [15, 16]. Broad QRS complexes suggest an antidromic circus movement tachycardia, which correlates with a higher likelihood of multiple than single accessory pathways [17]. A  $\Delta$ -wave is a qualitative ECG feature that reliably indicates preexcitation, whereas PQ-time should be interpreted with caution since cardiac anoxia could increase the PQ-interval [18] and administration of adrenalin could shorten it. In our case, the presence of a normal rather than a shortened PQ-time suggests a fasciculoventricular rather than a nodoventricular accessory bundle [19]. Functional left bundle branch blocks are typ-

ical in WPW [20] but no morphological correlate was found in this case.

We identified two parahissian accessory pathways, an atriofascicular and a fasciculoventricular pathway. Multiple pathways are associated with a higher risk of VF than single pathways [21], particularly when located in the posterior septum such as in this instance. They are found in 9% of pediatric patients with WPW syndrome [22]. However, ECG or electrophysiological testing do not necessarily diagnose any of the accessory pathways present, particularly in metabolically well-balanced individuals, where such pathways may remain silent for many years. As WPW may run in families in an autosomal dominant way [23], establishing a correct diagnosis at autopsy could help identifying risk groups before first symptoms manifest themselves as serious or lethal arrhythmia in surviving relatives.

Anatomically receding accessory pathways were suggested to be a temporary complication of cardiac development [5], which would explain why arrhythmia commonly associated with accessory pathways in newborns has been observed to resolve spontaneously within a year [24]. In

this male infant, death was preceded by a mild illness over several days: mild diarrhea, vomiting, and poor fluid intake without notable dehydration probably triggered reentry tachycardia and atrial fibrillation on the basis of activated accessory pathways.

Whenever death in previously asymptomatic carriers of a peculiarity, such as accessory bundles, but including others, is precipitated through dehydration [25], changes in diet [20], exercise [26], restraint [27], hypokalemia [28], catecholamines [29], or emotional stress [30], legal categorization of the death can be controversial [31]. In this instance, absence of perceptible dehydration led to the conclusion of natural death as a consequence of WPW syndrome. There was no prior indication that mild dehydration would have been detrimental to the child prior to death other than the palpitations the mother had noted.

In interpreting findings as to the cause and manner of death, exclusion of violence [32, 33, 34] and toxicological factors [35] as well as elucidation of legal responsibility [36] represent crucial steps in forensic cardiac conduction system pathology particularly in infant deaths without a prior history [37]. A full medicolegal investigation into deaths as a consequence of WPW syndrome should take into account that there are diagnostic and therapeutic options, as clinical identification of accessory pathways and antiarrhythmic medication [38] or catheter ablation are routine today even in infants [39].

Full 3D assessment of connectivity of dispersed tissue in pathological anatomy of the cardiac conduction system has the potential to match clinical accuracy in diagnosing accessory pathways [40] or exceed it in the posteroseptal region and in instances of multiple pathways which can be difficult to localize electrophysiologically [41]. Therefore, the technique presented provides an essential tool for forensic conduction system pathology [42] and a relevant complement to modern cardiac investigative morphology such as the search for early vital reactions to myocardial infarction [43, 44, 45, 46].

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